



Nihon Validation Technologies Corporation  
Tsunehiro Harada Ph.D. Senior Scientist

## Investigation of co-crystallization using carbamazepine

### Experiment

Crystal 16 was used to study the formation of co-crystals with Carbamazepine as a sample compound. When the mixing ratio of Carbamazepine and co-former was changed (by changing the mole fraction), and the possibility of co-crystallization was investigated by observing how the saturation temperature (Ts) changed, a stable region (where Ts increased) appeared, inferring the formation of co-crystals.

\*Information on sample compounds

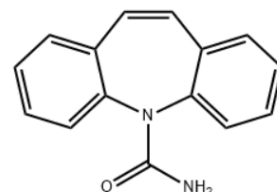
#### Carbamazepine (CBZ)

CAS No.: 298-46-4

Chemical formula : C<sub>15</sub>H<sub>12</sub>N<sub>2</sub>O

Molecular weight: 236.27

Solubility: 25 mg/mL (25°C) in EtOH Value on solubility curve



#### Co-formers

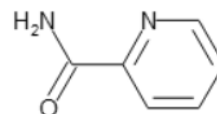
Picolinamide (PA)

CAS Number : 1452-77-3

Chemical formula : C<sub>6</sub>H<sub>6</sub>N<sub>2</sub>O

Molecular weight: 122.13

Solubility: 150 mg/mL (25°C) in EtOH Value on solubility curve



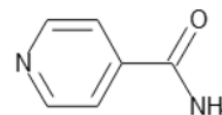
Isonicotinamide (INA)

CAS Number : 98-92-0

Chemical formula : C<sub>6</sub>H<sub>6</sub>N<sub>2</sub>O

Molecular weight: 122.13

Solubility: 70 mg/mL (25°C) in EtOH Value on solubility curve



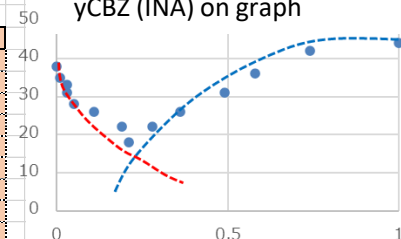
### 1. Preparation of measurement sample

Fourteen different EtOH solutions were prepared in conformance with the red portions of the table below.

In the case of CBZ-INA

CBZ and INA		$\chi_{CBZ} / \chi_{CBZ}^*(T) + \chi_{INA} / \chi_{INA}^*(T) = 1$				$y_{CBZ} = \chi_{CBZ} / (\chi_{CBZ} + \chi_{INA})$			
	Ts	$\chi_{CBZ}^*(T)$	$\chi_{CBZ}$	$\chi_{INA}^*(T)$	$\chi_{INA}$	$y_{CBZ}$		CBZ(mg)	INA(mg)
1	44	0.050/236	0.050/236	-	0	1		50	0
2	42	0.048/236	0.045/236	0.120/122	0.008/122	0.74		45	8
3	36	0.040/236	0.035/236	0.10/122	0.013/122	0.58		35	13
4	31	0.038/236	0.031/236	0.09/122	0.017/122	0.49		31	17
5	26	0.031/236	0.023/236	0.08/122	0.021/122	0.36		23	21
6	22	0.025/236	0.017/236	0.07/122	0.022/122	0.28		17	22
7	18	0.022/236	0.013/236	0.06/122	0.025/122	0.21		13	25
8	22	0.025/236	0.014/236	0.07/122	0.031/122	0.19		14	31
9	26	0.031/236	0.011/236	0.08/122	0.052/122	0.11		11	52
10	28	0.035/236	0.009/236	0.08/122	0.059/122	0.05		9	59
11	31	0.038/236	0.007/236	0.09/122	0.073/122	0.03		7	73
12	33	0.039/236	0.005/236	0.10/122	0.087/122	0.03		5	87
13	35	0.040/236	0.003/236	0.11/122	0.102/122	0.01		3	102
14	38	0.042/236	0	0.12/122	0.120/122	0		0	120

Relation between Ts and yCBZ (INA) on graph



A graph of Ts and yCBZ was generated using the values in the table. If no co-crystallization occurs, the dissolution temperature of each yCBZ sample should be similar to the above curve.

\* : The saturation mole fraction of each component at the indicated temperature. Ts values are read from the graph of the solubility curve of each component.

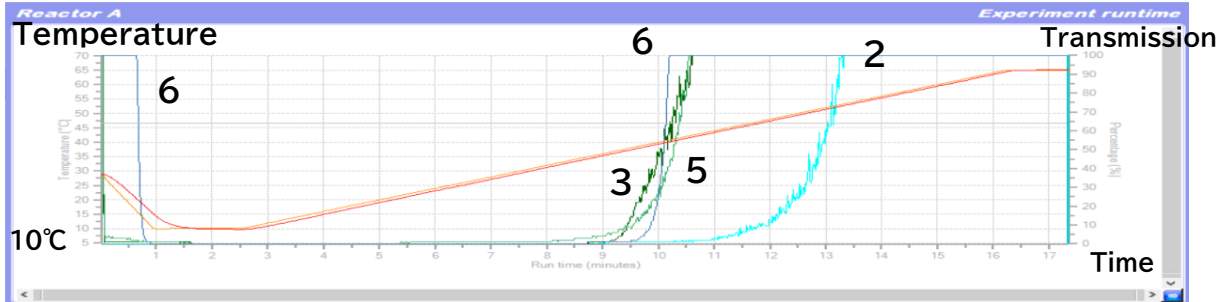


## 2. Selection of measurement conditions

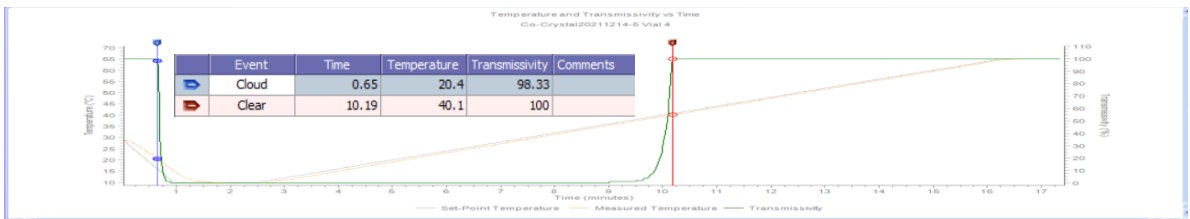
A total of 10 to 12 different sample solutions were used for each combination and measurement started from 10°C. The temperature was raised to 65°C at 4°C/min and the experiment was terminated after waiting for 1 minute.

## 3. Measurement results

C16 Example of measurement screenshot for CBZ-INA (sample numbers: 2, 3, 5, 6)

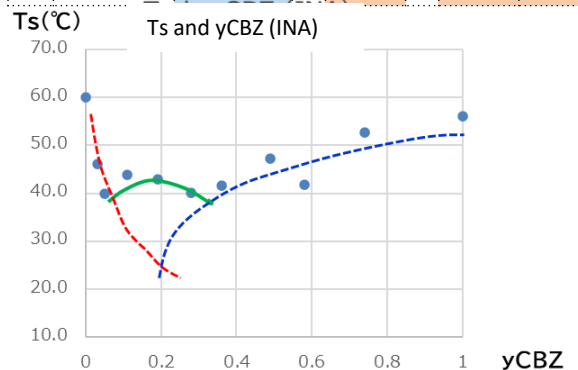
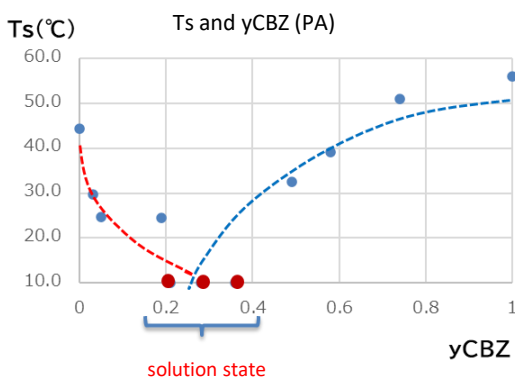


### CrystalClear Analysis Example (CBZ-INA Sample No. 6)



	Ts (predicted value)	Ts (actual measured value)	yCBZ	CBZ(m g)	PA(mg )
1	44	56.0	1	50	0
2	42	51.0	0.64	45	13
3	36	39.1	0.44	35	23
4	31	32.6	0.31	30	34
5	26	10.0	0.26	24	34
6	22	10.0	0.18	18	42
7	18	10.0	0.12	14	51
8	22	24.5	0.10	14	62
9	26	28.8	0.06	11	103
11	31	29.7	0.03	7	131
14	38	44.4	0	0	210

	Ts (predicted value)	Ts (actual measured value)	yCBZ	CBZ(m g)	INA(m g)
1	44	56.0	1	50	0
2	42	52.7	0.74	45	8
3	36	41.9	0.58	35	13
4	31	47.3	0.49	31	17
5	26	41.6	0.36	23	21
6	22	40.1	0.28	17	22
8	22	42.9	0.19	14	31
9	26	43.8	0.11	11	52
10	28	39.9	0.05	9	59
11	31	46.2	0.03	7	73
14	38	60.1	0	0	120



# Investigation of co-crystallization using Carbamazepine

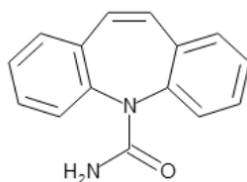
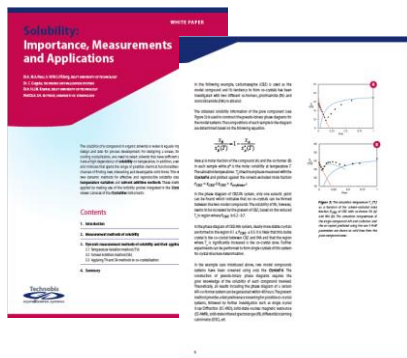
## Result:

In the case of CBZ and INA, for a sample with a  $y_{CBZ}$  of approximately 0.2, a solution was obtained after mixing and stirring for a while, and new crystals were then precipitated. The crystals dissolved at approximately 45°C. Co-crystal formation was therefore considered to have occurred. Under the same conditions no crystal precipitation was observed for CBZ and PA near  $y_{CBZ}$  0.2.

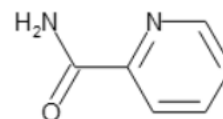
## Next steps

We plan to compare the respective Raman spectra of CBZ, INA, and precipitated crystals.

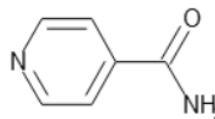
## Reference data (manufacturer's announcement)



CBZ (carbamazepine)

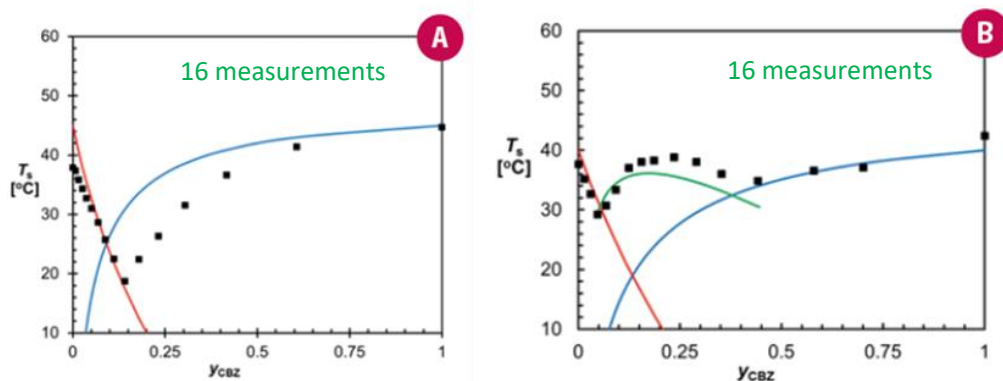


PA (picolinamide)



INA (isonicotinamide)

$$Y_{CBZ} = X_{CBZ} / (X_{CBZ} + X_{co-former})$$



**Figure 5:** The saturation temperature  $T_s$  [°C] as a function of the solvent-excluded mole fraction  $y_{CBZ}$  of CBZ with co-former PA (a) and INA (b). The saturation temperatures of the single-component API and co-former and the co-crystal predicted using the van 't Hoff parameters are shown as solid lines from the pure-component axes.

